Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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SARS-CoV-2: A new virus but a familiar inflammation brain pattern

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Dear Editor,

Two recent articles (Wu et al., 2020; Ye et al., 2020) published in your valuable journal have described encephalitis in course of Covid-19. With great interest I read those articles and herein I provide some food for thought to question raised by authors about unclear immunological findings of Central Nervous System (CNS) involvement in course of Covid-19.

Although the majority of Coronavirus infections of humans are associated with upper respiratory tract infections, in the past several laboratories have attempted to correlate inflammatory neurological disease with Coronavirus infection. However, the accumulated data suggest that the human Coronavirus are capable of infecting CNS. In the past, Murray et al. (1992) have shown that, during the acute phase, murine Coronavirus can replicate and cause direct lysis of oligodendrocytes and final demyelination in the CNS of human primates. Furthermore TNF-alfa, Il-1beta and Il-6 were measured to be increased in the spinal cord of infected mice. Butler et al. (2006) showed that in mice infected intranasally with neurovirulent strains of HCoV-OC43, virus enters the CNS via the olfactory nerves with subsequent transneuronal retrograde dissemination to distant connections of the olfactory bulb and primarily infects pyriform cortex and brainstem. Along with previous findings on Coronavirus, it is reasonable to think that SARS-CoV-2 enters the CNS via the olfactory bulb and may reach brainstem causing disfunction and/or death of infected neurons, especially those located in cardiorespiratory centers in the medulla. Along with previous investigations, Coronavirus infection of human CNS seems to be restricted to neurons and the lack of inflammation in infected brains raises the possibility that neurons die by apoptosis, a form of cell death associated with minimal cellular infiltration. Whether this occurs in infected subjects and interferes with initiation of the immune response is not known at present but it may be one mechanism that would result in a diminished inflammatory response.

Furthermore neurons do not normally express MHC class I or II antigen and express only low levels of the machinery required for loading peptide onto MHC class I antigen. However, neuronal production of IL-6 in vivo following viral infection has been previously reported (Netland et al, 2008). It is also possible that excessive levels of proinflammatory cytokines/chemokines in the brain result in a "cytokine storm" and lethal disease. It is well established that excessive production of cytokines can lead to harmful effects in the brain and other tissues. An excessive and possibly dysregulated cytokine response has been implicated in neuronal death and death of the animal in an experimental model of Japanese encephalitis virus infection and it has also been implicated in patients with SARS. Lending support to this hypothesis, three cytokines are often associated with inflammation in SARS-Cov-2 patients: IL-1, tumor necrosis factor alpha, and IL-6.

Together, these data suggest that anosmia (about half of patients with COVID-19 present with anosmia) can be an early indicator of CNS involvement in course of COVID-19. Thus, physicians should be aware about more probable worsening of clinical conditions, especially do to the fact that SARS-CoV-2 can itself causes an important respiratory insufficiency, together with the possible depression of cardiorespiratory centers.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.04.066.

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